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# The Interplay between Brain-Derived Neurotrophic Factors and Stress Hormone Modulates the Process of Neurogenesis

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**Abstract**

Alteration in neurogenesis plays a vital role in etiology of brain disease, including mental disorders and neurodegenerative diseases. The brain-derived neurotrophic factor (BDNF) is a key regulator of neural survival, growth and plasticity involved in emotional and cognitive function. It is a well-known neurotropic factor which is involved in neurogenesis process. BDNF is highly vulnerable to stress. Various evidences show a negative impact of the stress hormone glucocorticoids (GCs) on differentiation and survival of neurons, which is also related to the pathophysiology of brain diseases. This review article has demonstrated functional interactions between neurotropic factors and stress hormone in neurogenesis.

**Keywords:** BDNF; Neurotropic factor; Stress; Glucocorticoids; Neurodegeneration

## Introduction

Brain-derived neurotrophic factor (BDNF) is molecule that enhances the growth and maintenance of neurons in the central nervous system [1,2]. BDNF is highly expressed in the hippocampal and cortical regions of the brain where they involved in neuronal survival, synaptic plasticity and the formation of long-lasting memories [3-5]. Their high affinity receptor, TrkB has been identified as the Trk family of tyrosine protein kinases, thus facilitate to understand the signaling pathways responsible for mediating their trophic properties [6]. TrkB receptor is phosphorylated by binding of BDNF that trigger the activation of ERK-, Akt-, and PLC gamma-pathways [7-9]. Each pathway contributes to multifarious neuronal functions, including neurogenesis and the regulation of cell fate [10,11]. Various studies demonstrated that reduced expression of BDNF along with depressive behaviors, suggesting that an alteration in status of the BDNF/TrkB system leads to reduction in neurogenesis resulting brain dysfunctioning. Chronic stress reduces mRNA levels of BDNF [10,12] is one of the most important endogenous mediators of stress responses in the mammalian brain. Glucocorticoids (GCs) a stress hormone, exert influence on neurogenesis and functions, as well as BDNF [13]. Blood levels of GCs are regulated by hypothalamus-pituitary-adrenal (HPA) axis activity [14-16]. It is well known that chronic stress induces the hyper activation of HPA axis, resulting overabundance of GCs levels [16].

Elevated levels of GCs have a role in the onset of mental disorders, including post-traumatic stress disorder, major depressive disorders and neurodegeneration. Furthermore, GC stress suppress the formation of neuron synthesis, especially in hippocampal region, has been a vulnerable target to develop new drugs because it shows the dysregulation of HPA axis function [17,18] and is considered as a culprit that leads to the onset of the mental disorders [19]. This review article demonstrated the functional interaction between BDNF and GCs towards altered neurogenesis.

## Impact of BDNF and GCs on Brain

It is well known that chronic stress affects the neural morphology particularly in the hippocampus and the amygdala brain regions [20]. A single exposure to emotional stress is sufficient to increase dendritic length and number in amygdala region and vice versa in the hippocampus region [21,22]. Moreover, a study suggests that distinctive hippocampal and amygdala neuroarchitecture alteration predicting specific patterns of behavioral disruption following stress exposure in an animal [23]. These findings direct our focusing to understand if these stress effects on brain morphology are mediated by GCs. However, neurotrophic and GCs systems both act in antagonistic as well as in synergistic manners. BDNF and GC are involved in dendritic ramification, usually BDNF is associated with spine

formation and stabilization with GC rather playing a vital role in spine turnover [3,24]. A study showed that chronic GC administration results in spine loss in the cortex. Interestingly, transient raise in GC levels mostly affected newly formed spines, whereas chronically increased GCs affected spines that have been formed early in life [25].

However, both BDNF/TrkB and GCs/GR systems are occupied in neurogenesis, the interaction between these systems in neurogenesis is of interest. Therefore, this interplay in the neural function, including neurotransmitter release, synaptic structure has been investigated [18]. Many studies demonstrated a negative impact of systemic administration of GCs on BDNF mRNA expression in hippocampal and cortical regions [26-28]. It has been demonstrated that mRNA expression of BDNF was concealed by GC vulnerability via binding of GR to the regulatory sequences of the BDNF gene in neuron-like cells inveterate from mouse [29]. Previous study reported that TrkB also interacted with GR and mediated calcium signaling regulated by PLC gamma [29,30].

## Molecular Mechanisms of BDNF and GC Interplay

BDNF can directly influence the HPA-axis regulation through modification of CRH expression levels. On the other hand, dexamethasone (DEX, a synthestic GC) administration led to suppression of CRH, which could not be up to the mark by BDNF treatment [3]. A study revealed that DEX treatment stimulates more GR-binding to the CRH promoter [3,31]. In contrast to DEX, BDNF boost cAMP response element-binding protein (CREB) -binding to its site on the CRH promoter, which is in juxtaposition to the GR-binding site [32]. The central mechanistic element in CRH regulation is the recruitment of CREB to the CRH promoter. CREB requires the interaction with a coactivator protein named CREB regulated transcription coactivator 2 (CRTC2) for its transcriptional activity [33]. Upregulated GC levels lead to the relocalization of the nuclear CRTC2 to the cytosol and thus downregulate the CREB transcriptional activity at the CRH promoter [3]. In additional, another aspect of association between the GC- and BDNF-signaling pathways seems to involve the mitogen-activated protein kinase (MAPK) pathway. Overexpression of MKP-1 induces detrimental effects by obstruct the axonal growth [34]. Regulation of the GC levels and consecutively MKP-1 expression levels proceed towards the restoration of stress-related depressive phenotypes through regulate the BDNF expression [35]. In a further study it was demonstrated that acute GC activity excites transient enhancement in tissue-plasminogen activator protein, which is play a vital role in proteolytic cleavage of pro-BDNF to mature BDNF. The excessive amounts of mature BDNF itself associate with TrkB and trigger downstream MAPK phosphorylation, which is imperative for the emergence contextual fear memory [36].

## Conclusion

This review introduced the functional interplay between the BDNF/TrkB and GCs/GR systems in the neurogenesis. High level of BDNF and low GC levels are involved in neuronal maintenance, synaptic integrity and dendritic spine stabilization in the brain regions. BDNF-GC equilibrium is pivotal throughout life as a considerable mechanism for stress response regulation.

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## Conflicts of Interest

The authors declare no conflict of interest.

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